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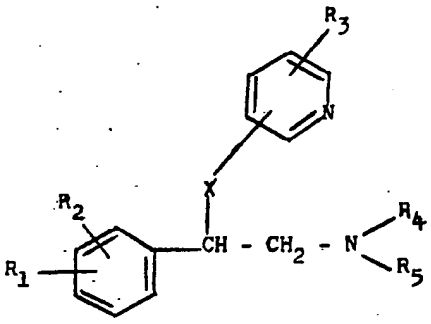
(54) 2,2-Disubstituted-ethylamines

(57) Substituted 2-phenyl-2-(pyridyloxy)-ethylamines and isosteric compounds of general formula



(I)

wherein
R_1 and R_2, which may be the same or different, each represents a hydrogen or halogen atom or a methyl, methoxy, amino or nitro group;
R_3 represents a hydrogen or halogen atom or a methyl group;
R_4 and R_5, which may be the same or different, either each represents a hydrogen atom or an alkyl group with 1 or 2 carbon atoms or, together with the nitrogen atom to which they are attached they may form a pyrrolidino or morpholino ring, and
X represents O, HN or S;
and acid addition salts thereof.

The new compounds are highly effective antidepressants with a structure hitherto unknown in this field of application.

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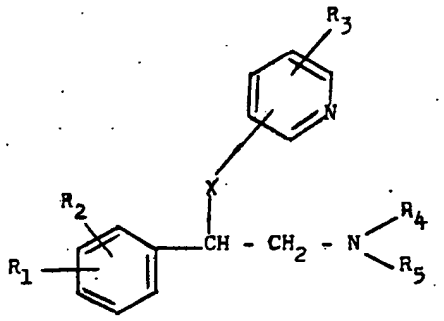
SPECIFICATION

2,2-Disubstituted-ethylamines

The invention relates to new substituted 2-phenyl-2-(pyridyloxy)-ethylamines and isosteric compounds, to processes for their preparation, to pharmaceutical compositions containing them and to their use as antidepressants.

According to one feature of the present invention there are provided substituted 2-phenyl-2-(pyridyloxy)-ethylamines and isosteric compounds of general formula



(I)

wherein

R_1 and R_2, which may be the same or different, each represents a hydrogen or halogen atom or a methyl, methoxy, amino or nitro group;

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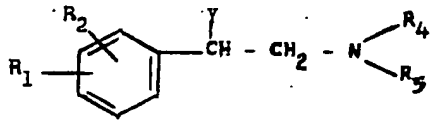
R_4 and R_5, which may be the same or different, either each represents a hydrogen atom or an alkyl group with 1 or 2 carbon atoms or, together with the nitrogen atom to which they are attached they may form a pyrrolidino or morpholino ring, and

X represents O, HN or S;

and acid addition salts thereof.

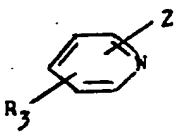
These compounds acording to the invention possess interesting pharmaelogical properties and in particular a useful antidepressant activity. It will be appreciated that, for pharmaceutical use, the salt referred to above will be physiologically compatible but other salts may find use, for example, in the preparation of compounds of general formula I and their physiologically compatible salt.

The new compounds may be obtained by reacting a phenyethylamine of formula



(II)

(wherein R_1, R_2, R_4 and R_5 are as hereinbefore defined and Y represents a halogen atom or a hydroxy group), or an acid addition salt of this compound, with a pyridine derivative of formula



(III)

(wherein R_3 is as hereinbefore defined and Z represents a hydroxy, amino or mercapto group) followed, if desired, by conversion of the product thus obtained into an acid addition salt thereof.

In the case of starting materials of general formula II wherein Y represents a hydroxy group, condensation is preferably effected with a compound of formula III in an acidic medium at elevated temperatures. For this reaction, it is possible to use strong inorganic or organic acids, e.g. concentrated mineral acids such as for example hydochloric acid, hydrobromic acid, sulphuric acid, or polyphosphoric acid and also acetic anhydride, phosphorus pentoxide or trifluoracetic acid.

Phenylethylamines of general formula II wherein Y represents a halogen atom are preferably reacted with the pyridine derivative of formula III in the presence of a base and preferably under

phase transfer conditions (i.e. with the addition of one or more long-chained tertiary amines such as e.g. a benzyl-tributyl-ammonium halide or a tetrabutyl-ammonium halide or using benzyl-triphenyl-phosphonium chloride).

Suitable bases include, for example, inorganic bases such as e.g. alkali and alkaline earth metal hydroxides and carbonates and organic bases such as e.g. pyridine, piperdine, tertiary amines and alkali metal alkoxides.

Compounds according to the invention wherein R_4 and/or R_5 represent hydrogen may be alkylated in a manner known *per se*, e.g. by reacting them with a dialkyl sulphate or an alkyl halide, to give the corresponding compound wherein R_5 and/or R_5 represents an alkyl group with 1 or 2 carbon atoms.

Using the process described above, the following end products may, for example, be obtained optionally in the form of their acid addition salts:

2-phenyl-2-(pyridyl-(3)-oxy)-N,N-dimethyl-ethylamine,
2-phenyl-2-(pyridyl-(2)-oxy)-N,N-dimethyl-ethylamine,
2-(p-bromophenyl)-2-(pyridyl-(2)-oxy-N,N-dimethyl-ethylamine;
2-(p-bromophenyl)-2-(pyridyl-(3)-oxy)-N,N-dimethyl-ethylamine;
2-(p-bromophenyl)-2-(2-chloropyridyl-(3)-oxy)-N,N-dimethyl-ethylamine,
2-(p-bromophenyl)-2-(5-chloro-pyridyl-(2)-oxy)-N,N-dimethyl-ethylamine,
2-(p-bromophenyl)-2-(6-chloro-pyridyl-(2)-oxy)-N,N-dimethyl-ethylamine,
2-(p-bromophenyl-2-(pyridyl-(4)-oxy)-N,N-dimethyl-ethylamine,
2-(p-chlorophenyl)-2-(pyridyl-(3)-oxy)-N,N-dimethyl-ethylamine,
2-(m,p-dichlorophenyl)-2-(pyridyl-(3)-oxy)-N,N-dimethyl-ethylamine,
2-phenyl-2-(pyridyl-(2)-amino)-N,N-dimethyl-ethylamine,
2-phenyl-2-(pyridyl-(3)-amino)-N,N-dimethyl-ethylamine,
2-(p-bromophenyl)-2-(pyridyl-(2)-amino-N-methyl-ethylamine,
2-(p-bromophenyl)-2-(pyridyl-(2)-amino)-N,N-dimethyl-ethylamine,
2-(p-bromophenyl)-2-(pyridyl-(3)-amino)-N,N-dimethyl-ethylamine,
2-phenyl-2-(4-methyl-pyridyl-(2)-amino)-N,N-dimethyl-ethylamine,
2-(p-bromophenyl)-2-(5-methyl-pyridyl-(2)-amino)-N,N-dimethyl-ethylamine,
2-(p-bromophenyl)-2-(6-methyl-pyridyl-(2)-amino)-N,N-dimethyl-ethylamine,
2-(4-p-bromophenyl)-2-(5-chloro-pyridyl-(2)-amino)-N,N-dimethyl-ethylamine,
2-(4-p-bromophenyl)-2-(pyridyl-(2)-thio)-N,N-dimethyl-ethylamine,
2-(p-bromophenyl)-2-(pyridyl-(3)-oxy)-morpholino-ethylamine,
2-(p-bromophenyl)-2-(pyridyl-(3)-oxy)-pyrrolidino-ethylamine,
2-(p-bromophenyl)-2-(pyridyl-(2)-amino)-morpholino-ethylamine,
2-(p-bromophenyl)-2-(pyridyl-(2)-amino)-pyrrolidino-ethylamine,
2-(p-methoxyphenyl)-2-(pyridyl-(3)-oxy)-N,N-dimethyl-ethylamine,
2-(p-hydroxyphenyl)-2-(pyridyl-(3)-oxy)-N,N-dimethyl-ethylamine,
2-(p-tolyl)-2-(pyridyl-(3)-oxy)-N,N-diethyl-ethylamine,
2-(p-nitrophenyl)-2-(pyridyl-(2)-oxy)-N,N-dimethyl-ethylamine,
2-(4-aminophenyl)-2-(pyridyl-(2)-oxy)-N,N-dimethyl-ethylamine,
2-(m,p-dichlorophenyl)-2-(pyridyl-(3)-amino)-N,N-dimethyl-ethylamine,
2-(m,p-dimethoxyphenyl)-2-(pyridyl-(3)-oxy)-N,N-dimethyl-ethylamine.

The starting materials are widely used chemicals which may be obtained commercially or can be prepared using methods which are generally known.

The end products of general formula I may, if desired, be converted into the acid addition salts thereof by conventional methods.

Suitable acids include both inorganic acids such as e.g. hydrohalic acids, sulphuric, phosphoric and amino-sulphonic acid, and also organic acids such as e.g. formic, acetic, propionic, lactic, glycolic, gluconic, maleic, succinic, tartaric, benzoic, salicylic, citric, ascorbic, p-toluenesulphonic and oxyethane sulphonic acid.

As mentioned above the compounds of general formula I and the acid addition salts thereof possess interesting pharmacological properties. Those which we have tested have proved highly effective in biochemical and pharmacological test systems specific to antidepressants. Thus, they are capable of inhibiting the ptosis induced in the mouse by tetrabenzain; the ED_{50} is of the order of 1 mg/kg. This test is used as a standard for antidepressant properties (International Journal of Neuropharmacology *8*, 73 (1968)).

The compounds according to the invention have also shown an exceptionally favourable activity in the test for reserpine antagonism, namely the reversal of the hypothermic effect caused by reserpine by means of a substance with an antidepressant activity. It has also been found that they inhibit the re-absorption of serotonin and adrenalin into the neurones.

The new compounds are particularly useful in that they have a different structure from the antidepressants known up to now; they are equivalent or superior to known commercially available products in their activity but have a lower toxicity.

Particular mention should be made of compounds of general formula I wherein R_1 represents a bromine atom in the p-position, X represents an oxygen atom or the amino group, R_2 represents hydrogen and R_3 and R_4 represent methyl groups. Particular mention should be made of the compounds:

2-(p-bromophenyl)-2-(pyridyl-(3)-oxy)-N,N-dimethyl-ethylamine,
2-(p-bromophenyl-2-(pyridyl-(2)-amino)-N,N-dimethyl-ethylamine,
2-(p-bromophenyl)-2-pyridyl-(3)-amino)-N,N-dimethyl-ethylamine.

According to a yet further feature of the present invention there are provided phamaceutical compositions comprising as active ingredient, at least one compound of formula I as hereinbefore defined or a physiologically compatible acid addition salt thereof in association with a pharmaceutical carrier or excipient.

For pharmaceutical administration the compounds of general formula I and their physiologically compatible acid addition salts may be incorporated into the conventional preparations in either solid or liquid form, optionally in combination with other active ingredients. The compositions may, for example, be presented in a form suitable for oral administration. Preferred forms include, for example tables and coated tablets

The active ingredient may be incorporated in excipients customarily employed in pharmaceutical compositions such as, for example, talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, aqueous or non-aqueous vehicles, fatty substances of animal or vegetable origin, paraffin derivatives, glycols, various wetting, dispersing or emulsifying agents and/or preservatives,

Advantageously the compositions may be formulated as dosage units, each unit being adapted to supply a fixed dose of active ingredient.

The following non-limiting examples serve to illustrate the present invention.

Example 1

2-p-Bromophenyl-2-(pyridyl-(3)-oxy)-N,N-dimethyl-ethylamine dihydrochloride

29.9 g of 2-chloro-2-p-bromophenyl-N,N-dimethyl-ethylamine hydrochloride (0.1 mol) and 14.3 g of 3-hydroxypridine (0.15 mol) are refluxed for 16 hours in 150 ml of 25% sodium hydroxide solution and 150 ml of toluene with 0.5g of benzyltriphenyl phosphonium chloride. After the solvent has been distilled off from the organic phase a residue is left which is dissolved in alcohol. The dihydrochloride of the title compound is obtained with hydrochloric acid. For purification, the title compound is treated in cyclohexane with active charcoal and kieselguhr. The yield of dihydrochloride is 20 g (44% of theory).
Melting point 128–129°C (ethanol).

Example 2

2-p-Bromophenyl-2-(pyridyl-(2)-amino)-N,N-dimethyl-ethylamine-dioxalate

24.5 g of 2-p-bromophenyl-N,N-dimethylethanolamine (0.1 mol) and 11 g of 2-aminopyridine (0.11 mol) are heated to 60°C for 30 minutes in 50 ml of methanesulphonic acid. Whilst still warm, the reaction mixture is poured on to ice, made alkaline with ammonia and extracted with ethyl acetate. The product is purified by column chromatography over silicia gel/methylene chloride-ethyl acetate-methanol. The crystalline dioxalate of the title compound is obtained by the addition of alcoholic oxalic acid.
The yield is 21 g (42% of theory). Melting point 170–171°C.

The following compounds of general formula I were obtained using the process described hereinbefore:

Example No.	R_1	R_2	R_3	R_4	R_5	X	Pyridyl bond	Mp°C
3	4-Br	H	H	H	Ch3	NH	2	181–182
4	H	H	H	CH_3	CH_3	O	2	161–162
5	H	H	H	CH_3	CH_3	O	3	151–152
6	H	H	H	CH_3	CH_3	NH	2	129–130
7	H	H	H	CH_3	CH_3	NH	3	123–125
8	4-Br	H	2-Cl	CH_3	CH_3	O	3	135–136
9	4-Br	H	5-Cl	CH_3	CH_3	O	2	234–235
10	4-Br	H	6-Cl	CH_3	CH_3	O	2	193–194
11	H	H	4-CH_3	CH_3	CH_3	NH	2	139–140
12	4-Br	H	5-Cl	CH_3	CH_3	NH	2	134–136
13	4-Br	H	5-CH_3	CH_3	CH_3	NH	2	103–104
14	4-Br	H	6-CH_3	CH_3	CH_3	NH	2	135–136
15	4-Br	H	H	CH_3	CH_3	NH	3	144–145
16	4-Br	H	H	CH_3	CH_3	O	2	162–163
17	4-Br	H	H	CH_3	CH_3	S	2	190–191
18	4-Br	H	H	Morpholine		O	3	95–97
19	4-Br	H	H	Morpholine		NH	2	194–195
20	4-Br	H	H	Pyrrolidine		O	3	152–153
21	4-Br	H	H	Pyrrolidine		NH	2	117–119
22	4-Br	H	H	CH_3	CH_3	O	4	112 (decomp)
23	4-Cl	H	H	CH_3	CH_3	O	3	126–129 (decomp)
24	3-Cl	4-Cl	H	CH_3	CH_3	O	3	175–176
25	4-OCH_3	H	H	CH_3	CH_3	O	3	103–105
26	3-Cl	4-Cl	H	CH_3	CH_3	NH	3	152–153
27	3-OCH_3	H	H	H	H	O	3	222–223
28	4-CH_3	H	H	CH_3	CH_3	O	3	180–181
29	4-Br	H	4-CH_3	CH_3	CH_3	NH	2	219–220

Examples of Formulation

a) *Coated tablets*

1 tablet core contains:

Active substance according to the invention	25.0 mg
Lactose	50.0 mg
Corn starch	22.0 mg
Gelatine	2.0 mg
Magnesium stearate	1.0 mg
	100.0 mg

Preparation:

The mixture of active substance, lactose and corn starch is granulated with a 10% aqueous gelatine solution through a screen with a 1 mm mesh, then dried at 40°C and again passed through a screen. The granulate thus obtained is mixed with a magnesium stearate and compressed. The cores thus obtained are coated in the usual way with a coating which is applied using an aqueous suspension of sugar, titanium dioxide, talc and gum arabic. The finished coated tablets are polished with beeswax.

Final weight of coated tablet: 200 mg

b) *Tablets*

Active substance according to the invention	10.0 mg
Lactose	40.0 mg
Corn starch	44.0 mg
Soluble starch	5.0 mg
Magnesium stearate	1.0 mg
	100.0 mg

Method:

The active substance and magnesium stearate are granulated with an aqueous solution of the soluble starch, the granulate is dried and intimately mixed with lactose and corn starch. The mixture is then compressed to form tablets weighing 100 mg and each containing 10 mg of active substance.

c) *Suppositories*

1 Suppository contains:

Active substance according to the invention	10.0 mg
Suppository mass	1,690.0 mg

Method:

Using an immersion homogeniser, the finely powdered substance is stirred into the molten suppository mass which has been cooled to 40°C. At 35°C the mass is poured into slightly pre-cooled moulds.

d) *Ampoules (Injection solutions)*

Composition:

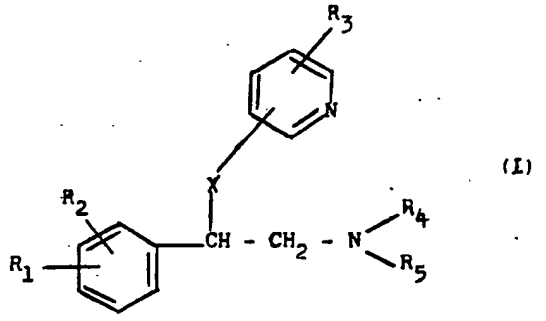
Active substance according to the invention	5.0 parts by weight
Sodium pyrosulphite	1.0 parts by weight
Disodium salt of ethylene-diamine tetraacetec acid	0.5 parts by weight
Sodium chloride	8.5 parts by weight
Doubly distilled water *ad*	1,000 parts by weight

Method

The active substance and excipients are dissolved in sufficient water and adjusted to the desired concentration with the required amount of water. The solution is filtered and transferred into 1 ml ampoules under aseptic conditions. Finally the ampoules are sterilised and sealed. Each ampoule contains 5.0 mg of active substance.

CLAIMS

1. Substituted 2-phenyl-2-(pyridyloxy)-ethylamines and isosteric compounds of general formula



(I)

wherein

R_1 and R_2, which may be the same or different, each represents a hydrogen or halogen atom or a methyl, methoxy, amino or nitro group;

R_3 represents a hydrogen or halogen atom or a methyl group;

R_4 and R_5, which may be the same or different, either each represents a hydrogen atom or an alkyl group with 1 or 2 carbon atoms or, together with the nitrogen atom to which they are attached they may form a pyrrolidino or morpholino ring, and
X represents O, NH or S;
and acid addition salts thereof.

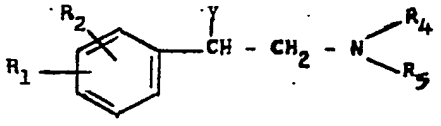
2. 2-(p-Bromophenyl)-2-(pyridyl-(3)-oxy)-N,N-dimethyl-ethylamine and acid addition salts thereof.

3. 2-(p-Bromophenyl)-2-(pyridyl-(2)-amino)-N,N-dimethyl-ethylamine and acid addition salts thereof.

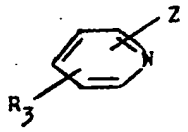
4. 2-(p-Bromophenyl-2-(pyridyl-(3)-amino)-N,N-dimethyl-ethylamine and acid addition salts thereof.

5. Physiologically compatible acid addition salts of compounds of general formula I as defined in claim 1.

6. Process for the preparation of compounds as claimed in claim 1 which comprises reacting a phenylethylamine of formula


(II)

(wherein R_1, R_2, R_4 and R_5 are as defined in claim 1 and Y represents a halogen atom or a hydroxy group) or an acid addition salt of this compound, with a pyridine derivative of formula


(III)

(wherein R_3 is as defined in claim 1 and Z represents a hydroxy, amino or mercapto group) followed, if desired, by conversion of the product thus obtained into an acid addition salt thereof.

7. Process as claimed in claim 6 wherein, in the compound for formula II, Y represents a hydroxy group and the reaction is effected in an acidic medium at elevated temperatures.

8. Process as claimed in claim 6 wherein, in the compound of formula II, Y represents a halogen atom and the reaction is effected in the presence of a base.

9. Process for the preparation of compounds as claimed in claim 1 wherein R_4 and/or R_5 represents an alkyl group with 1 or 2 carbon atoms which comprises alkylating a compound as claimed in claim 1 wherein R_4 and/or R_5 represents a hydrogen atom.

10. Process as claimed in claim 9 wherein alkylation is effected by means of a dialkyl sulphate or an alkyl halide.

11. Process for the preparation of compounds as claimed in claim 1 substantially as herein discribed.

12. Process for the preparation of compounds as claimed in claim 1 substantially as herein described in any one of Examples 1–29.

13. Process for the preparation of compounds as claimed in claim 1 substantially as herein described in any one of Examples 1–26.

14. Compounds as claimed in claim 1 whenever prepared by a process as claimed in any one of claims 6 to 12.

15. Compounds of general formula I as claimed in claim 1 and physiologically compatible acid addition salts thereof for use as antidepressants.

16. Phamaceutical compositions comprising, as active ingredient, at least one compound of formula I as defined in claim 1 or a physiologically compatible acid addition salt thereof in association with a pharmaceutical carrier or excipient.

17. Compositions as claimed in claim 16 in the form of dosage units.

18. Pharmaceutical compositions as claimed in claim 16 substantially as herein described.

19. Pharmaceutical compositions substantially as herein described in Formulation examples (a) - (d).

20. A method of treating a patient suffering from or susceptible to depression which comprises administering to the said patient an effective amount of a compound of formula I as defined in claim 1 or a physiologically compatible acid addition salt thereof.

21. Each and every novel method, process, compound and composition herein disclosed.

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